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Aromatic heterocyclic biaryl compounds, pharmaceutical and cosmetic compositio ns containing them and uses thereof

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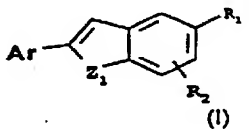
ABSTRACT

AROMATIC HETEROCYCLIC BIARYL COMPOUNDS, PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING THEM AND USES THEREOF

The invention relates to novel aromatic heterocyclic biaryl compounds which have the general formula (I):



(I)

and to the use of these compounds in pharmaceutical compositions intended for use in human or veterinary medicine (dermatological, rheumatic, respiratory, cardiovascular and ophthalmological complaints in particular), or alternatively in cosmetic compositions.

AUSTRALIA

Patents Act 1990

COMPLETE SPECIFICATION

STANDARD PATENT

Applicant(s):

GALDERMA RESEARCH & DEVELOPMENT, S.N.C.

Invention Title:

AROMATIC HETEROCYCLIC BIARYL COMPOUNDS, PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING THEM AND USES THEREOF.

The following statement is a full description of this invention, including the best method of performing it known to me/us:

AROMATIC HETEROCYCLIC BIARYL COMPOUNDS, PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING THEM AND USES THEREOF

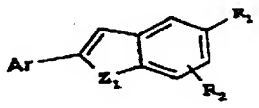
The invention relates to, as novel and useful industrial products, aromatic heterocyclic biaryl compounds. It also relates to the use of these novel compounds in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions.

The compositions according to the invention have pronounced activity in the fields of cell differentiation and proliferation and find applications more particularly in the topical and systemic treatment of dermatological (or other) complaints associated with a keratinization disorder, complaints with an inflammatory and/or immunoallergic component and hyperproliferation of tissues of ectodermal origin (skin, epithelium, etc.), whether they are benign or malignant. These compounds can also be used in the treatment of diseases of degeneration of connective tissue, to combat ageing of the skin, whether this is light-induced or chronological ageing, and to treat cicatrization disorders. They find an application in particular in ophthalmology in the treatment of corneopathies.

The compounds according to the invention can also be used in cosmetic compositions for body and hair

hygiene.

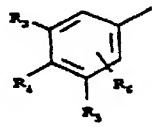
The present invention relates to compounds which can be represented by the general formula (I) below:



I

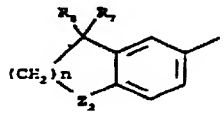
in which,

Ar represents a radical chosen from the radicals of formulae (II)-(IV) below:



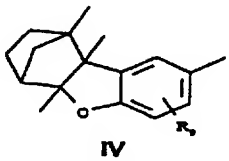
II

R_3, R_4, R_5 and R_6 having the meanings given below,



III

n, Z_2, R_7 and R_8 having the meanings given below,



IV

R_9 having the meaning given below,

Z_1 represents an oxygen or sulphur atom or a radical NR',

R' having the meaning given below,

Z_2 represents $C(R_7R_8)$, O, NR', S, SO or SO_2,

R_7, R_8 and R' having the meanings given below,

R_1 represents

(i) a $-CH_3$ radical,

(ii) a radical $-(CH_2)_m-O-R_{10}$,

(iii) a radical $-CH_2-O-CO-R_{11}$

(iv) a radical $-(CH_2)_x-CO-R_{12}$

(v) a radical $-(CH_2)_x-CO-OR_{13}$

R_{10}, R_{11}, R_{12} and R_{13}, m, x and t having the meanings given below,

R_2 represents a hydrogen atom, a halogen atom, a linear or branched alkoxy radical of 1 to 20 carbon atoms or an $-O-CH_2-O-CH_2-CH_2-O-CH_3$ radical,

R_3 and R_5, which may be identical or different, represent a hydrogen atom, an alkyl radical or a cycloalkyl radical,

with the following conditions:

- R_3 and R_5 do not simultaneously represent a hydrogen atom,
- when R_3 or R_5 represents an adamantyl radical, then Z_1 is other than an oxygen atom,

R_4 represents an $-O-CH_2-O-CH_2-CH_2-O-CH_3$ radical, a radical $-(Y)_q-(CH_2)_s-R_{14}$, a radical $-(CH_2)_z-Y-(CH_2)_s-R_{14}$ or a radical $-CH=CH-(CH_2)_w-R_{14}$,

Y and R_{14} having the meanings given below,

q, z, s, w, which may be identical or different, having the meanings given below,

R_6 represents a hydrogen atom, a halogen atom, a linear or branched alkoxy radical of 1 to 20 carbon atoms or a radical $-O-CH_2-O-CH_2-CH_2-O-CH_3$,

R_7 and R_8, which may be identical or different, represent a lower alkyl radical,

R_9 represents a hydrogen atom, a halogen atom, a linear or branched alkoxy radical of 1 to 20 carbon atoms or an $-O-CH_2-O-CH_2-CH_2-O-CH_3$ radical,

R_{10} represents a hydrogen or a lower alkyl radical,

R_{11} represents a lower alkyl radical,

R_{12} represents a hydrogen atom, a lower alkyl radical or a radical -N(R",R"'),

R" and R"' having the meanings given below,

R_{13} represents a hydrogen atom, a linear or branched alkyl radical of 1 to 20 carbon atoms, an alkenyl radical or a mono- or polyhydroxyalkyl radical,

R_{14} represents a radical chosen from:

(i) a hydrogen atom,

(ii) a lower alkyl radical,

(iii) an alkenyl radical,

(iv) an alkynyl radical,

(v) a cycloaliphatic radical containing from 3 to 6 carbon atoms,

(vi) a mono- or polyhydroxyalkyl radical, it being possible for the hydroxyl groups to be

optionally protected in the form of methoxy, acetoxy or acetonide,

(vii) a radical $CO-R_{12}$,

(viii) a radical $COO-R_{13}$,

(ix) a hydroxyl radical, a radical $O-R_{15}$ or $O-CO-R_{15}$, on the condition that R_4 represents a radical $-(Y)_q-(CH_2)_s-R_{14}$ where q is equal to 0,

Y and R_{15} having the meanings given below,

q and s having the meanings given below,

R_{15} represents a lower alkyl radical,

R' represents a hydrogen atom, a lower alkyl radical or a protecting group for the amine function,

R" and R"', which may be identical or different, represent a hydrogen atom, a lower alkyl radical or a mono- or polyhydroxyalkyl radical, or alternatively R" and R"', taken together, form a heterocycle,

Y represents S, O or S(O)t,

t having the meaning given below,

m represents an integer which can take a value ranging from 0 to 2,

n represents an integer which can take the value 1 or 2,

q represents an integer which can take the value 0 or 1,

s represents an integer which can take a value ranging from 0 to 12,

t represents an integer which can take a value ranging from 0 to 3,

w represents an integer which can take a value ranging from 0 to 10,

x represents an integer which can take a value ranging from 0 to 2,

z represents an integer which can take the value 1, 2 or 3.

The invention is also directed towards the optical or geometrical isomers of the said compounds of formula (I), as well as the salts thereof.

When the compounds according to the invention are in the form of salts by addition of a base, these are salts of an alkali metal or alkaline-earth metal or alternatively of zinc or of an organic amine.

When the compounds are in the form of salts, by addition of an acid, they are pharmaceutically or cosmetically acceptable salts obtained by addition of an inorganic or organic acid, in particular hydrochloric acid, sulphuric acid, acetic acid, citric acid, fumaric acid, hemisuccinic acid, maleic acid or mandelic acid.

According to the present invention, the expression "lower alkyl radical" means a linear or branched radical containing from 1 to 6 carbon atoms, and preferably the methyl, ethyl, isopropyl, n-butyl and tert-butyl radicals.

The expression "alkyl radical" means a linear

or branched radical containing from 1 to 20 carbon atoms, optionally substituted with one or more halogen atoms, and preferably the methyl, ethyl, isopropyl, butyl, tert-butyl and hexyl radicals.

The expression "alkenyl radical" means a linear or branched radical containing from 1 to 20 carbon atoms and one or more double bonds.

The term "alkynyl radical" means a linear or branched radical containing from 1 to 20 carbon atoms and one or more triple bonds.

Among the halogen atoms, a fluorine, chlorine or bromine atom is preferred.

The expression "protecting group for an amine function" means the corresponding groups described in "Protecting Groups in Organic Synthesis" by T.W. Greene, published by John Wiley and Sons (1981), and preferably a formamide, acetamide, chloracetamide, trifluoroacetamide or benzyloxycarbonyl group.

The expression "cycloalkyl radical" means a cyclic or polycyclic alkane radical containing from 1 to 10 carbon atoms, optionally substituted with:

- one or more halogen atoms,

and/or

- one or more hydroxyl radicals.

The cycloalkyl radical is preferably chosen from an adamantyl radical and a 1-methylcyclohexyl radical.

The expression "monohydroxyalkyl radical" means a radical containing from 1 to 6 carbon atoms, in

particular a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical.

Among the linear or branched alkoxy radicals containing from 1 to 20 carbon atoms, radicals of 1 to 9 carbon atoms are preferred, in particular the methoxy, propyloxy, pentyloxy and heptyloxy radicals.

The expression "polyhydroxyalkyl radical" means a radical containing from 1 to 6 carbon atoms and from 1 to 5 hydroxyl groups, such as the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl and 2,3,4,5-tetrahydroxypentyl radicals or a pentaerythritol residue.

The term "heterocycle" preferably means a piperidino, morpholino, pyrrolidino or piperazino radical, optionally substituted in position 4 with a C_1-C_6 alkyl radical or a mono- or polyhydroxyalkyl radical as defined above.

The expression "cycloaliphatic radical containing from 3 to 6 carbon atoms" preferably means a cyclopropyl radical or a cyclohexyl radical.

Among the compounds falling within the scope of the present invention, mention may be made in particular of the following:

- methyl 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)furancarboxylate,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)furancarboxylic acid,
- methyl 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-

2-naphthyl)-5-benzo(b)thiophenecarboxylate,

- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)thiophenecarboxylic acid,

- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-indolecarboxylic acid,

- methyl 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-indolecarboxylate,

- 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)benzo(b)thiophene-5-carboxylic acid,

- methyl 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)-benzo(b)thiophene-5-carboxylate,

- 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)benzo(b)furan-5-carboxylic acid,

- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-methoxy-2-naphthyl)-5-benzo(b)furancarboxylic acid,

- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-methoxy-2-naphthyl)-5-benzo(b)thiophenecarboxylic acid,

- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-n-propyloxy-2-naphthyl)-5-benzo(b)thiophenecarboxylic acid,

- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-n-propyloxy-2-naphthyl)-5-benzo(b)furancarboxylic acid,

- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-n-heptyloxy-2-naphthyl)-5-benzo(b)furancarboxylic acid.

According to the present invention, the

compounds of formula (I) which are more particularly preferred are those for which at least one, and preferably all, of the following conditions are satisfied:

- R_1 is a radical $-(CH_2)_x-CO-R_{12}$ or $-(CH_2)_x-CO-O-R_{13}$
- R_2 is a hydrogen,
- Z_1 is an oxygen or sulphur atom
- Ar is chosen from

the radical IV in which:

- R_9 is a hydrogen atom

or the radical III in which:

- Z_2 is a radical $C(R_7, R_8)$
- n=2

A subject of the present invention is also processes for preparing compounds of formula (I), in particular according to the reaction schemes given in Figures 1 and 2.

Thus, the compounds of general formula (I) can be obtained (Figure 1) by the method of type A.

This method consists in reacting a derivative (V) bearing an alcohol, thiol or amine function with an aromatic derivative bearing an activated carboxylic function (VI), Ar having the meaning described in the general formula (I).

The intermediate compound obtained VII is then subjected to a radical bromination reaction to give the derivative VIII.

After reaction in the presence of a triarylphosphine or a trialkyl phosphite, the resulting derivatives are cyclized in basic medium. The base can be an alkali metal hydroxide or carbonate such as lithium hydroxide or potassium carbonate, an alkali metal hydride (sodium hydride), an alkali metal alkoxide (sodium methoxide), a tertiary amine (DBU, diazabicycloundecene) or an alkali metal amide (lithium diisopropylamide).

The compounds of general formula (I) can also be obtained (Figure 2) by the method of type B.

In this method, the derivatives are obtained by a "one-pot" reaction between an activated form of the aromatic carboxylic acid **VI** and an aromatic derivative of formula **IX** bearing an alcohol, thiol or amino function ortho to a methyltriphenylphosphonium bromide group. This reaction is carried out in the presence of a tertiary amine such as triethylamine.

The products of general formula (I) obtained in this way may serve as starting materials for the manufacture of other compounds of general formula (I). These products are obtained according to the standard synthetic methods employed in chemistry, such as those described in "Advanced Organic Chemistry" by J. March; John Willey and Sons, 1985.

For example, functional modifications of the group R_1 may be performed as indicated below:

carboxylic acid -> ester
ester -> carboxylic acid
acid -> acid chloride
acid chloride -> amide
acid -> amide
acid -> alcohol
alcohol -> aldehyde
amide -> amine
thiol -> thioether
thioether -> sulphoxide
thioether -> sulphone
sulphonic acid -> sulphonic ester
sulphonic acid -> sulphonamide
sulphinic acid -> sulphinic ester

The compounds of general formula (I) exhibit agonist or antagonist activity towards the expression of one or more biological markers in the test of differentiation of mouse embryonic teratocarcinoma cells (F9) (Skin Pharmacol. 3, p.256-267, 1990) and/or on the in vitro differentiation of human keratinocytes (Skin Pharmacol. 3 p.70-85, 1990). These abovementioned tests show the activities of the compounds in the fields of differentiation and proliferation. The activities may also be measured in tests of cell transactivation using recombinant RAR receptors according to the method of B.A. Bernard et al., Biochemical and Biophysical Research Communication 1992, vol. 186, 977-983.

The subject of the present invention is also, as medicinal product, the compounds of formula (I) as described above.

The compounds according to the invention are particularly suitable in the following fields of treatment:

1) For treating dermatological complaints linked to a keratinization disorder which has a bearing on differentiation and on proliferation, in particular for treating common acne, comedones, polymorphonuclear leukocytes, acne rosacea, nodulocystic acne, acne conglobata, senile acne and secondary acnes such as solar, medicational or occupational acne.

2) For treating other types of keratinization disorder, in particular ichthyoses, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leukoplasias and leukoplasiform states, and cutaneous or mucous (buccal) lichen.

3) For treating other dermatological complaints associated with a keratinization disorder with an inflammatory and/or immunoallergic component and, in particular, all forms of psoriasis, whether this is cutaneous, mucous or ungual psoriasis, and even psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema or respiratory atopy or even gingival hypertrophy; the compounds may also be used in certain inflammatory complaints which do not exhibit any keratinization disorder.

4) For treating all dermal or epidermal proliferations, whether these are benign or malignant and whether or not they are of viral origin, such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatoses and proliferations which may be induced by ultraviolet radiation, in particular in the case of basocellular and spinocellular epithelioma.

5) For treating other dermatological disorders such as bullosis and collagen diseases.

6) For treating certain ophthalmological disorders, in particular corneopathies.

7) For repairing or combating ageing of the skin, whether this is photoinduced or chronological ageing, or for reducing actinic keratoses and pigmentations, or all pathologies associated with chronological or actinic ageing.

8) For preventing or curing the stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy.

9) For preventing or treating cicatrization disorders or for preventing or repairing stretchmarks.

10) For combating disorders of sebaceous function such as acneic hyperseborrhoea or simple seborrhoea.

11) In the treatment or prevention of cancerous or precancerous states, more particularly promyelocytic leukaemias.

12) In the treatment of inflammatory complaints such as arthritis.

13) In the treatment of any skin complaint or general complaint of viral origin.

14) In the prevention or treatment of alopecia.

15) In the treatment of dermatological or general complaints having an immunological component.

16) In the treatment of complaints of the cardiovascular system such as arteriosclerosis.

In the therapeutic fields mentioned above, the compounds according to the invention can advantageously be used in combination with other retinoids, with RXR receptor ligands, with vitamin D derivatives, with corticosteroids or oestrogens, in combination with antioxidants, with α-hydroxy or α-keto acids or derivatives thereof, or alternatively with potassium-channel blockers.

The expression "RXR receptor ligand" means either 9-cis retinoic acid or a synthetic analogue which binds to these RXRs.

The expression "D vitamins or derivatives thereof" means, for example, derivatives of vitamin D_2 or D_3 and in particular 1,25-dihydroxyvitamin D_3.

The expression "anti-free-radical agents" is understood to refer, for example, to α-tocopherol, superoxide dismutase, ubiquinol or certain metal-chelating agents.

The expression "α-hydroxy or α-keto acids or

derivatives thereof" is understood to refer, for example, to lactic acid, maleic acid, citric acid, glycolic acid, mandelic acid, tartaric acid, glyceric acid, ascorbic acid or salicylic acid derivatives or salts, amides or esters thereof.

The expression "potassium-channel blockers" is understood to refer, for example, to Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and derivatives thereof.

The subject of the present invention is also medicinal compositions containing at least one compound of formula (I), as defined above, one of the optical or geometrical isomers thereof or one of the salts thereof.

The subject of the present invention is thus also a novel medicinal composition intended in particular for the treatment of the abovementioned complaints, characterized in that it contains, in a pharmaceutically acceptable support, at least one compound of formula (I), one of the optical or geometrical isomers thereof or one of the salts thereof.

The pharmaceutical compositions according to the invention may be administered via the enteral, parenteral, topical or ocular route.

Via the enteral route, the medicinal products may be in the form of tablets, gelatin capsules, coated tablets, syrups, suspensions, solutions, powders,

granules, emulsions, microspheres or nanospheres or polymeric or lipid vesicules allowing controlled release. Via the parenteral route, the compositions may be in the form of solutions or suspensions for infusion or for injection.

The compounds according to the invention are generally administered at a daily dose of about 0.01 mg/kg to 100 mg/kg of body weight taken 1 to 3 times.

Via the topical route, the pharmaceutical compositions based on compounds according to the invention are intended for treating the skin and the mucous membranes and are in the form of ointments, creams, milks, salves, powders, impregnated pads, solutions, gels, sprays, lotions or suspensions. They may also be in the form of microspheres or nanospheres or polymeric or lipid vesicules or polymeric patches and hydrogels allowing controlled release. These topical route compositions may be either in anhydrous form or in aqueous form depending on the clinical indication.

Via the ocular route, these compositions are mainly eye drops.

These compositions for the topical or ocular route contain at least one compound of formula (I) as defined above, one of the optical or geometrical isomers thereof or one of the salts thereof, at a concentration preferably of between 0.001 and 5% relative to the total weight of the composition.

The compounds of formula (I), according to the invention, also find application in the cosmetic field, in particular in body and hair hygiene and especially for the treatment of skin with a tendency to develop acne, for the regrowth of the hair, to prevent hair loss, to control the greasy appearance of the skin or the hair, in protecting against the harmful effects of the sun or in the treatment of physiologically dry skin, and for preventing and/or combating photoinduced or chronological ageing.

In the cosmetic field, the compounds according to the invention may advantageously be employed in combination with other retinoids, with D vitamins or derivatives thereof, with corticosteroids, in combination with anti-free-radical agents, with α-hydroxy or α-keto acids or derivatives thereof, or alternatively with ion-channel blockers.

The various products taken in combination with the compounds of the present invention are as defined above.

The present invention is thus also directed towards a cosmetic composition containing, in a cosmetically acceptable support, at least one compound of formula I, one of the optical or geometrical isomers thereof or one of the salts thereof, this composition being in particular in the form of a cream, a milk, a lotion, a gel, microspheres or nanospheres or polymeric or lipid vesicules, a soap or a shampoo.

The concentration of compound of formula (I) in the cosmetic compositions is between 0.001 and 3% by weight.

The medicinal and cosmetic compositions according to the invention may, in addition, contain inert or even pharmacodynamically or cosmetically active additives or combinations of these additives and, in particular: wetting agents; depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizing agents such as glycerol, PEG 400, thiamorpholinone and derivatives thereof or urea; antiseborrhoea or antiacne agents such as *S*-carboxymethylcysteine, S-benzylcysteamine, salts thereof and derivatives thereof, or benzoyl peroxide; antibiotics such as erythromycin and esters thereof, neomycin, clindamycin and esters thereof, and tetracyclins; antifungal agents such as ketoconazole or poly-4,5-methylene-3-isothiazolinones; agents which promote the regrowth of the hair, such as Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and derivatives thereof, diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and phenytoin (5,4-diphenylimidazolidine-2,4-dione); non-steroidal antiinflammatory agents; carotenoids and, in particular, β-carotene; antipsoriasis agents such as anthralin and derivatives thereof and, lastly, eicosa-5,8,11,14-tetraynoic acid and eicosa-5,8,11-triynoic acid, amides and esters thereof.

The compositions according to the invention may also contain agents for improving the flavour, preserving agents such as para-hydroxybenzoic acid, stabilizers, humidity regulators, pH regulators, osmotic pressure modifiers, emulsifying agents, UV-A and UV-B screening agents, and antioxidants such as α-tocopherol, butylhydroxyanisole or butylhydroxytoluene.

Several examples of the preparation of the active compounds of formula I of the invention will now be given, by way of illustration and with no limiting nature, along with examples of compositions containing them.

A. EXAMPLES OF COMPOUNDS

1) ACCORDING TO THE SYNTHETIC ROUTE ILLUSTRATED BY FIGURE 1

Example 1: methyl 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)furancarboxylate

a) 3-Methyl-4-hydroxybenzoic acid

32.4 g of ortho-cresol are mixed with 375 ml (1.87 mol) of 5N sodium hydroxide, followed by addition of 25 g of β-cyclodextrin and 1.88 g of powdered copper metal. 65 ml (0.58 mmol) of carbon tetrachloride are added over 10 minutes and the mixture is heated at 80°C with stirring for 16 hours. The reaction medium is cooled and poured into an ice-cold 2N HCl mixture and is extracted with ethyl ether. The organic phase is washed with water, dried over magnesium sulphate,

filtered and evaporated. After purification on silica, eluting with pure ethyl ether, 40 g (88%) of a red solid is isolated, and is used directly for step 1b.

b) Methyl 3-methyl-4-hydroxybenzoate

The compound obtained in Example 1a is dissolved in 650 ml of methanol and treated with 10 ml of concentrated sulphuric acid and then refluxed for 16 hours.

After cooling, evaporation of the methanol and addition of water, the product is extracted with ethyl ether and the organic phase is washed with water, dried over magnesium sulphate and evaporated. The product is purified by chromatography on silica, eluting with the mixture: dichloromethane/ethyl ether (90:10) to give 33.1 g (76%) of a pink solid. ^{1}H NMR ($CDCl_3$) d 2.27 (s, 3H), 3.89 (s, 3H), 6.83 (d, 1H, J = 8.3 Hz), 7.79 (d, 1H, J = 8.3 Hz), 7.84 (s, 1H).

c) Methyl 3-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthoyloxy)benzoate

11.7 ml (160 mmol) of thionyl chloride are added dropwise to 18.6 g (80 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxylic acid and the medium is heated at 80°C for 2h 30. The reaction medium is evaporated to dryness and dissolved in 150 ml of anhydrous THF. The solution thus obtained is added dropwise to a solution, at 0°C, containing 13.3 g (80 mmol) of the phenol obtained in Example 1a and 12.3 ml (88 mmol) of triethylamine, in 50 ml of dry

THF. The reaction medium is stirred for 16h at room temperature, water is then added and the resulting mixture is extracted with ethyl ether. The organic phase is washed with water, dried over magnesium sulphate and evaporated. The residue obtained is purified on silica, eluting with a dichloromethane/hexane mixture (60:40) to give, after evaporation of the solvents, 15.6 g (51%) of the expected derivative, in the form of a white solid product. ^{1}H NMR ($CDCl_3$) d 1.33 (s, 6H), 1.35 (s, 6H), 1.73 (s, 4H), 2.28 (s, 3H), 3.92 (s, 3H), 7.21 (d, 1H, J = 8.4 Hz), 7.46 (d, 1H, J = 8.3 Hz), 7.92 to 7.99 (m, 3H), 8.17 (d, 1H, J = 1.8 Hz).

d) Methyl 3-bromomethyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyloxy)benzoate

3.1 g (17.35 mmol) of N-bromosuccinimide and a few crystals of benzoyl peroxide are added to a solution of 6 g (17.35 mmol) of the derivative obtained in Example 1c, in 70 ml of carbon tetrachloride, and the reaction medium is heated at 80°C for 8 hours. After cooling and addition of water, the product is extracted with dichloromethane and the organic phase is washed with water, dried over magnesium sulphate and evaporated. After purification on silica, eluting with hexane/ethyl acetate (93:7), 4.7 g (65%) of the expected derivative are isolated in the form of a solid white product. ^{1}H NMR ($CDCl_3$) d 1.34 (br d, 12H), 1.73 (s, 4H), 3.92 (s, 3H), 4.49 (s, 2H), 7.40 (d, 1H, J =

8.5 Hz), 7.48 (d, 1H, J = 8.3 Hz), 8.00 (dd, 1H, J = 8.3/1.9 Hz), 8.07 (dd, 1H, J = 8.5/1.9 Hz), 8.17 (d, 1H, J = 1.7 Hz), 8.26 (d, 1H, J = 1.7 Hz).

e) Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-benzo(b)furancarboxylate

4.7 g (10.23 mmol) of the derivative obtained in Example 1d, dissolved in 40 ml of anhydrous THF, are treated with 3.1 g (11.7 mmol) of triphenylphosphine and heated at 80°C for 4 hours. After cooling to room temperature, 1.76 ml (11.7 mmol) of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) are added dropwise, the mixture is stirred for one hour at 35°C, acidified to pH 1 (2N HCl) and then extracted with ethyl ether. After extraction with ethyl ether, the usual work-up of the organic phase and evaporation, the product is purified on silica in a hexane/dichloromethane mixture (60:40) to give, after evaporation, 2.5 g (67%) of the expected derivative in the form of a solid white product. ^{1}H NMR ($CDCl_3$) d 1.31 (s, 6H), 1.37 (s, 6H), 1.72 (s, 4H), 3.94 (s, 3H), 7.01 (s, 1H), 7.39 (d, 1H, J = 8.3 Hz), 7.54 (d, 1H, J = 8.7 Hz), 7.60 (dd, 1H, J = 8.3/1.8 Hz), 7.81 (d, 1H, J = 1.8 Hz), 8.00 (dd, 1H, J = 8.6/1.7 Hz), 8.29 (d, 1H, J = 1.3 Hz).

Example 2: 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-benzo(b)furancarboxylic acid

2.5 g (6.9 mmol) of the compound obtained in Example 1 are placed in 160 ml of methanol and are treated with 13.8 ml of 5N sodium hydroxide (69 mmol).

The reaction mixture is refluxed for 2 hours. After cooling, evaporation of the methanol and acidification, the residue obtained is extracted with ethyl ether. The organic phase is then washed with water, dried and evaporated to give 2.4 g (100%) of the expected derivative in the form of a white solid melting at 273°C. ^{1}H NMR (DMSO d_6) d 1.27 (s, 6H), 1.33 (s, 6H), 1.67 (s, 4H), 7.46 (d, 1H, J = 8.3 Hz), 7.53 (s, 1H), 7.67 (dd, 1H, J = 8.3/1.3 Hz), 7.73 (d, 1H, J = 8.6 Hz), 7.86 (d, 1H, J = 1.5 Hz), 7.93 (dd, 1H, J = 8.6/1.6 Hz), 8.27 (d, 1H, J = 1.2 Hz), 12.93 (s, 1H).

Example 3: Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-benzo(b)thiophenecarboxylate

3a) Methyl 3-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-benzo(b)thiophenecarboxylate

21.9 ml (110 mmol) of dicyclohexylamine are added dropwise to a solution containing 23.2 g (100 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxylic acid in 100 ml of dichloromethane. The reaction medium is stirred for 30 min at room temperature and the dichloromethane is then evaporated off and the residue is taken up in 200 ml of ethyl ether. The precipitate is dried, 6.8 g (16.5 mmol) of this salt are then dissolved in 20 ml of dichloromethane and 1.9 ml (26.3 mmol) of thionyl chloride are added dropwise. The reaction medium is stirred at room temperature for 15 hours. After filtering off the dicyclohexylamine hydrochloride, the

reaction medium is evaporated and the acid chloride obtained is then taken up in 30 ml of anhydrous THF. A cold solution composed of 3 g (16.5 mmol) of methyl 3-methyl-4-mercaptobenzoate and 2.52 ml (18.1 mmol) of triethylamine dissolved in 10 ml of dry THF is then added dropwise. The reaction medium is stirred for one hour at room temperature, water is then added and the product is extracted with ethyl ether. After the usual work-up of the organic phase and purification on silica in the eluent hexane/dichloromethane (50:50), 5.77 g (88%) of the expected product are isolated in the form of a white solid. ^{1}H NMR ($CDCl_3$) d 1.31/1.33 (d, 12H), 1.72 (s, 4H), 3.94 (s, 3H), 7.43 (d, 1H, J = 8.3 Hz), 7.57 (d, 1H, J = 8.0 Hz), 7.81 (dd, 1H, J = 8.3/2.0 Hz), 7.90 (dd, 1H, J = 8.0/2.0 Hz), 7.97 (d, 1H, J = 1.9 Hz), 8.02 (d, 1H, J = 2.0 Hz).

3b) Methyl 3-bromomethyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoylthio)benzoate

5.77 g (14.5 mmol) of the derivative obtained in Example 3a are dissolved in 70 ml of carbon tetrachloride, 2.72 g (15.3 mmol) of N-bromosuccinimide are added and the reaction medium is refluxed for 6 hours. After cooling and addition of water, the product is extracted with dichloromethane and the organic phase is worked-up conventionally. After chromatography on silica in a 90:10 hexane/ethyl acetate mixture, 5 g (72%) of the expected product are isolated in the form of a white solid. ^{1}H NMR ($CDCl_3$) d 1.31/1.33 (d, 12H),

1.72 (s, 4H), 3.95 (s, 3H), 4.62 (s, 2H), 7.44 (d, 1H, J = 8.3 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.82 (dd, 1H, J = 8.3/1.9 Hz), 7.98 (d, 1H, J = 1.9 Hz), 8.03 (dd, 1H, J = 8.1/1.8 Hz), 8.24 (d, 1H, J = 1.6 Hz).

3c) Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-benzo(b)thiophenecarboxylate

5 g (10.5 mmol) of the compound obtained in Example 3b, dissolved in 50 ml of anhydrous THF, are treated with 3.2 g (12.1 mmol) of triphenylphosphine and refluxed for 5 hours. After cooling to room temperature, 1.8 ml (12.1 mmol) of DBU are added dropwise and the mixture is stirred for one hour at 35°C, acidified to pH1 (2N HCl) and then extracted with ethyl ether. After the usual work-up of the organic phase and purification on silica in hexane/dichloromethane eluent (60:40), and after evaporation, 2.65 g (66%) of the expected derivative are obtained in the form of a white solid. ^{1}H NMR ($CDCl_3$) d 1.31 (s, 6H), 1.35 (s, 6H), 1.72 (s, 4H), 3.96 (s, 3H), 7.37 (d, 1H, J = 8.2 Hz), 7.47 (dd, 1H, J = 8.2/1.9 Hz), 7.54 (s, 1H), 7.63 (d, 1H, J = 1.8 Hz), 7.84 (d, 1H, J = 8.5 Hz), 7.95 (dd, 1H, J = 8.5/1.5 Hz), 8.46 (d, 1H, J = 0.9 Hz).

Example 4: 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-benzo(b)thiophenecarboxylic acid

The compound obtained in Example 3 (2.65 g; 7.0 mmol), dissolved in 150 ml of methanol, is treated with 14 ml (70 mmol) of 5N sodium hydroxide. The

mixture is refluxed for 2 hours. After cooling, evaporation of the methanol and acidification, the product is extracted with ethyl ether. After working up the organic phase, 2.36 g (92%) of the expected derivative are collected in the form of a solid white product melting at 244°C. ^{1}H NMR (DMSO d_6) d 1.26 (s, 6H), 1.32 (s, 6H), 1.57 (s, 4H), 7.42 (d, 1H, J = 8.3 Hz), 7.50 (d, 1H, J = 8.3 Hz), 7.70 (s, 1H), 7.90 (d, 1H, J = 8.4 Hz), 7.98 (s, 1H), 8.07 (d, 1H, J = 8.4 Hz), 8.46 (s, 1H), 13.03 (s, 1H).

Example 5: Methyl 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)-benzo(b)thiophene-5-carboxylate

5a) Methyl 3-methyl-4-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-carbonyl-thio)benzoate

8.5 g (18.7 mmol) of the dicyclohexylamine salt of -1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-carboxylic acid are converted into the acid chloride as described in the preparation of Example 3a and are dissolved in 40 ml of THF. This first solution is then added dropwise to a second, composed of 3.42 g (18.7 mmol) of 2-methyl-4-methoxy-carbonylthiophenol and 2.87 ml (20.6 mmol) of triethyl-amine in 12 ml of THF. The mixture is left stirring for 1h at room temperature, water is added and it is extracted with ethyl ether. After the usual work-up of the organic phase and chromatography in a dichloro-

methane/hexane mixture (50:50), 6.6 g (81%) of the expected derivative are isolated in the form of a solid white product. ^{1}H NMR ($CDCl_3$) d 0.86 to 1.68 (m, 6H), 1.21 (s, 3H), 1.27 (s, 3H), 1.39 (s, 3H), 2.28 (d, 1H, J = 4.1 Hz), 2.45 (s, 3H), 3.93 (s, 3H), 6.80 (d, 1H, J = 8.1 Hz), 7.57 (d, 1H, J = 8.1 Hz), 7.66 (d, 1H, J = 1.9 Hz), 7.90 (dd, 1H, J = 8.0/1.4 Hz), 7.95 (dd, 1H, J = 8.5/2.0 Hz), 8.01 (d, 1H, J = 2.0 Hz).

5b) Methyl 3-bromomethyl-4-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-carbonyl-thio)benzoate

The derivative obtained in Example 5a (5.84 g; 13.9 mmol), placed in 180 ml of carbon tetrachloride, is treated with 2.5 g (14.75 mmol) of N-bromosuccinimide. The reaction mixture is heated at 70°C for 24 hours to give, after the same work-up as in Example 1d, 2.2 g (32%) of the expected derivative in the form of a solid white product. ^{1}H NMR ($CDCl_3$) d 0.86 to 1.68 (m, 6H), 1.21 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 2.28 (d, 1H, J = 4.0 Hz), 3.95 (s, 3H), 4.64 (s, 2H), 6.81 (d, 1H, J = 8.5 Hz), 7.63 (d, 1H, J = 8.1 Hz), 7.66 (d, 1H, J = 1.9 Hz), 7.97 (dd, 1H, J = 8.5/1.9 Hz), 8.02 (dd, 1H, J = 8.1/1.8 Hz), 8.23 (d, 1H, J = 1.6 Hz).

5c) Methyl 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)-benzo(b)-thiophene-5-carboxylate

The compound obtained in Example 5b (2.2 g,

4.27 mmol), dissolved in 20 ml of THF, is treated with 1.3 g (4.9 mmol) of triphenylphosphene and then with 0.73 ml (4.9 mmol) of DBU, under the conditions described in Example 1. After the same work-up, followed by chromatography in a dichloromethane/hexane mixture (40:60), 0.64 g (36%) of the expected derivative is isolated in the form of a solid white product. ^{1}H NMR ($CDCl_3$) d 0.85 to 1.68 (m, 6H), 1.24 (s, 3H), 1.30 (s, 3H), 1.39 (s, 3H), 2.26 (d, 1H, J = 4.1 Hz), 3.96 (s, 3H), 6.79 (d, 1H, J = 8.3 Hz), 7.32 (d, 1H, J = 1.7 Hz), 7.44 (s, 1H), 7.50 (dd, 1H, J = 8.3/1.8 Hz), 7.82 (d, 1H, J = 8.4 Hz), 7.93 (dd, 1H, J = 8.5/1.4 Hz), 8.43 (d, 1H, J = 1.7 Hz).

Example 6: 2-(1,2,3,4,4a,9b-Hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)benzo(b)-thiophene-5-carboxylic acid

The compound obtained in Example 5 (0.64 g; 1.53 mmol) is placed in 35 ml of methanol and 100 ml of THF, 7.6 ml of 2N sodium hydroxide are then added and the mixture is heated at 40°C for 2 hours. After the same work-up as for the isolation of the compound of Example 1, followed by impasting in hexane, 0.54 g (87%) of the expected derivative is obtained in the form of a solid white product melting at 256°C. ^{1}H NMR (DMSO d_6) d 0.83 to 0.92 (m, 2H), 1.05 to 1.15 (m, 2H), 1.22 (s, 3H), 1.28 (s, 3H), 1.35 (s, 3H), 1.53 (m, 2H), 1.72 (d, 1H, J = 10.2 Hz), 2.20 (d, 1H, J = 3.2 Hz), 6.83 (d, 1H, J = 8.9 Hz), 7.52 to 7.54 (d + s, 2H),

7.84 to 7.88 (d + s, 2H), 8.04 (d, 1H, J = 8.4 Hz), 8.39 (s, 1H), 12.98 (s, 1H).

Example 7: 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthyl)-5-benzo(b)furancarboxylic acid

7a) 2-Methoxy-3-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylnaphthalene

40 g (162.3 mmol) of 2-hydroxy-3-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylnaphthalene are dissolved in 250 ml of DMF and are then cooled to 0°C. 5.12 g (170.5 mmol) of sodium hydride are then added slowly, followed by dropwise addition of 24.2 ml (170.5 mmol) of methyl iodide. The reaction mixture is left stirring overnight at room temperature and is then poured into ice-cold water. The mixture is extracted with ethyl ether and, after the usual work-up followed by chromatography in a dichloromethane/hexane mixture (40:60), 36.0 g (85%) of a crystalline off-white product are isolated. ^{1}H NMR ($CDCl_3$) d 1.27 (s, 6H), 1.30 (s, 6H), 1.68 (s, 4H), 2.59 (s, 3H), 3.89 (s, 3H), 6.85 (s, 1H), 7.73 (s, 1H).

7b) 2-Methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-3-carboxylic acid

91 g (570 mmol) of bromine are added to a solution of 440 ml of 5N sodium hydroxide, cooled to 0°C, followed by a solution of 35.9 g (138 mmol) of the compound obtained in Example 7a dissolved in 275 ml of dioxane. The reaction medium is stirred at room

temperature for 4 hours and is then neutralized with 5N HCl and extracted with ethyl ether. The organic phase is washed with water, with sodium thiosulphate, rinsed to neutral pH, dried and filtered, and the solvents are evaporated off. The product is purified on silica with ethyl ether/hexane (40:60) as eluent. 27.7 g (77%) of the expected derivative are obtained in the form of a pink-white solid. ^1H NMR ($CDCl_3$) d 1.28 (s, 6H), 1.31 (s, 6H), 1.69 (s, 4H), 4.06 (s, 3H), 6.93 (s, 1H), 8.12 (s, 1H).

7c) Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthyl)-5-benzo(b)furancarboxylate

5.25 g (20 mmol) of the acid obtained in Example 7b are converted into the acid chloride as described in Example 1c, and are dissolved in 90 ml of toluene. This solution is then added dropwise to a solution containing 10.65 g (21 mmol) of 2-hydroxy-4-methoxycarbonylbenzyltriphenylphosphonium bromide (obtained according to the method described in patent EP 732,328) and 7.6 ml (54.4 mmol) of triethylamine in 150 ml of toluene. The reaction mixture is refluxed for 15 minutes. It is cooled, taken up in ethyl ether, acidified with 2N HCl and extracted with ethyl ether. After the usual work-up of the organic phase and purification on silica with dichloromethane/hexane (60:40) as eluent, 2.95 g (38%) of a solid white product are obtained. ^1H NMR ($CDCl_3$) d 1.33 (s, 6H), 1.36 (s, 6H), 1.72 (s, 4H), 3.94 (s, 3H), 3.98 (s, 3H),

6.91 (s, 1H), 7.32 (s, 1H), 7.54 (d, 1H, J = 8.6 Hz), 7.96 (s, 1H), 7.99 (dd, 1H, J = 8.6/1.8 Hz), 8.30 (d, 1H, J = 1.2 Hz).

Example 8: 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthyl)-5-benzo(b)furancarboxylic acid

2.9 g (7.39 mmol) of the compound obtained in Example 7, dissolved in 160 ml of methanol, are treated with 15 ml of 5N sodium hydroxide solution under the conditions described for the synthesis of Example 2. After the same work-up, followed by recrystallization from an ethyl ether/hexane mixture (30:70), 2.43 g (87%) of a solid white product melting at 280°C are isolated. ^{1}H NMR ($CDCl_3$) d 1.33 (s, 6H), 1.36 (s, 6H), 1.72 (s, 4H), 3.99 (s, 3H), 6.91 (s, 1H), 7.32 (s, 1H), 7.54 (d, 1H, J = 8.6 Hz), 7.95 (s, 1H), 8.01 (dd, 1H, J = 8.6/1.7 Hz), 8.32 (d, 1H, J = 1.3 Hz).

Example 9: Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-n-propyloxy-2-naphthyl)-5-benzo(b)furancarboxylate

9a) 2-n-Propyloxy-3-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylnaphthalene

35.6 g (0.14 mol) of 2-hydroxy-3-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthyl-naphthalene, dissolved in 300 ml of DMF, are treated with 4.5 g of sodium hydride and then with 18.7 g of n-propyl bromide under the conditions described in Example 7a. After the same work-up and chromatography

on silica with ethyl ether/hexane (5:95) as eluent, 27.3 g (65%) of the expected derivative are isolated in the form of a white solid. ^1H NMR ($CDCl_3$) d 1.08 (t, 3H), 1.27 (s, 6H), 1.29 (s, 6H), 1.67 (s, 4H), 1.87 (m, 2H), 2.62 (s, 3H), 4.01 (t, 2H), 6.83 (s, 1H), 7.75 (s, 1H).

9b) 2-n-Propyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-3-carboxylic acid

27.3 g of the compound obtained in Example 9a, dissolved in 190 ml of dioxane, are treated with a sodium hypobromite solution consisting of 300 ml of 5N sodium hydroxide, placed at 0°C, and 62.4 g of bromine, under the conditions described in Example 7b. After the same work-up, 24.1 g (88%) of the expected compound are isolated in the form of a white solid. ^1H NMR ($CDCl_3$) d 1.10 (t, 3H), 1.28 (s, 6H), 1.30 (s, 6H), 1.69 (s, 4H), 1.94 (m, 2H), 4.20 (t, 2H), 6.91 (s, 1H), 8.12 (s, 1H), 11.06 (br s, 1H).

9c) Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-n-propyloxy-2-naphthyl)-5-benzo(b)furancarboxylate

5.8 g (20 mmol) of the acid obtained in Example 9b are converted into the acid chloride, as described in Example 1c, and are then treated with 10.65 g (21 mmol) of 2-hydroxy-5-methoxycarbonylbenzyl-triphenylphosphonium bromide and 7.6 ml (54.4 mmol) of triethylamine under the conditions described in Example 5 (synthesis of type b). After the same work-up, followed by chromatography on silica with dichloro-

methane/hexane (40:60) as eluent, 3.1 g (37%) of a solid white product are obtained. ^{1}H NMR ($CDCl_3$) d 1.15 (t, 3H), 1.32 (s, 6H), 1.36 (s, 6H), 1.71 (s, 4H), 1.97 (m, 2H), 3.94 (s, 3H), 4.09 (t, 2H), 6.89 (s, 1H), 7.36 (s, 1H), 7.54 (d, 1H, J = 8.6 Hz), 7.96 (s, 1H), 7.99 (dd, 1H, J = 8.6/1.6 Hz), 8.32 (d, 1H, J = 1.4 Hz).

Example 10: 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-n-propyloxy-2-naphthyl)-5-benzo(b)furancarboxylic acid

3.05 g (7.25 mmol) of the compound obtained in Example 9, dissolved in 160 ml of methanol, are treated with 14.5 ml of 5N sodium hydroxide in the conditions described in the synthesis of Example 2. After the same work-up, followed by recrystallization from an ethyl ether/hexane mixture (30:70), 2.7 g (92%) of a solid white product melting at 256°C are isolated. ^{1}H NMR ($CDCl_3$) d 1.15 (t, 3H), 1.32 (s, 6H), 1.36 (s, 6H), 1.72 (s, 4H), 1.98 (m, 2H), 4.10 (t, 2H), 6.89 (s, 1H), 7.35 (s, 1H), 7.54 (d, 1H, J = 8.6 Hz), 7.96 (s, 1H), 8.01 (dd, 1H, J = 8.6/1.7 Hz), 8.32 (d, 1H, J = 1.2 Hz).

Example 11: Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-n-heptyloxy-2-naphthyl)-5-benzo(b)furancarboxylate

11a) 2-n-Heptyloxy-3-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene

40 g (0.16 mol) of 2-hydroxy-3-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthyl-

naphthalene, dissolved in 350 ml of DMF, are treated with 5.1 g of sodium hydride and then with 26.8 ml of n-heptyl bromide under the conditions described in Example 7a. After the same work-up followed by chromatography on silica with dichloromethane/hexane (40:60) as eluent, 42.9 g (77%) of the expected product are isolated in the form of a yellow oil. ^{1}H NMR ($CDCl_3$) d 0.82 to 0.92 (m, 5H), 1.27 (s, 6H), 1.29 (s, 6H), 1.30 to 1.51 (m, 6H), 1.67 (s, 4H), 1.84 (m, 2H), 2.62 (s, 3H), 4.03 (t, 2H), 6.82 (s, 1H), 7.75 (s, 1H).

11b) 2-n-Heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-3-carboxylic acid

42.7 g of the compound obtained in Example 11a, dissolved in 250 ml of dioxane, are treated with a sodium hypobromite solution consisting of 397 ml of 5N sodium hydroxide, cooled to 0°C, and 81.8 g of bromine, under the conditions described in Example 7b. After the same work-up followed by chromatography on silica, 39.9 g (93%) of the expected derivative are isolated in the form of a solid white product. ^{1}H NMR ($CDCl_3$) d 0.90 (t, 3H), 1.28 (s, 6H), 1.30 (s, 6H), 1.30 to 1.49 (m, 8H), 1.69 (s, 4H), 1.91 (m, 2H), 4.22 (t, 2H), 6.91 (s, 1H), 8.12 (s, 1H).

11c) Methyl 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-n-heptyloxy-2-naphthyl)-5-benzo(b)furancarboxylate

6.9 g (20 mmol) of the acid obtained in Example 11b are converted into the acid chloride, as described in Example 1c, and are then treated with

10.65 g (21 mmol) of 2-hydroxy-5-methoxycarbonylbenzyl-triphenylphosphonium bromide and 7.6 ml (54.4 mmol) of triethylamine under the conditions described in Example 7c. After the same work-up followed by chromatography on silica with dichloromethane/heptane (35:65) as eluent, 3.8 g (40%) of a solid white product are obtained. ^{1}H NMR ($CDCl_3$) d 0.92 (t, 3H), 1.32 (s, 6H), 1.36 (s, 6H), 1.25 to 1.59 (m, 8H), 1.71 (s, 4H), 1.96 (m, 2H), 3.94 (s, 3H), 4.11 (t, 2H), 6.88 (s, 1H), 7.35 (s, 1H), 7.54 (d, 1H, J = 8.6 Hz), 7.96 (s, 1H), 7.99 (dd, 1H, J = 8.6/1.7 Hz), 8.31 (d, 1H, J = 1.2 Hz).

Example 12: 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-n-heptyloxy-2-naphthyl)-5-benzo(b)furancarboxylic acid

3.7 g (7.8 mmol) of the compound obtained in Example 11, dissolved in 160 ml of methanol, are treated with 15.7 ml of 5N sodium hydroxide, under the conditions described for the synthesis of Example 2. After the same work-up followed by recrystallization from an ethyl ether/hexane mixture, 3.5 g (98%) of a solid white product melting at 200°C are isolated. ^{1}H NMR ($CDCl_3$) d 0.93 (t, 3H), 1.33 (s, 6H), 1.37 (s, 6H), 1.34 to 1.61 (m, 8H), 1.72 (s, 4H), 1.96 (m, 2H), 4.12 (t, 2H), 6.89 (s, 1H), 7.38 (s, 1H), 7.59 (d, 1H, J = 8.6 Hz), 7.97 (s, 1H), 8.08 (dd, 1H, J = 8.6/1.7 Hz), 8.41 (d, 1H, J = 1.3 Hz).

Example 13: 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-indolecarboxylic acid

13a) Methyl 3-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylcarbonylamino)benzoate

5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenecarboxylic acid (37.7 g; 162.6 mmol) is converted into the acid chloride as indicated in Example 3a. After the same work-up, this acid chloride is added to a solution, cooled to 0°C, containing 25 g (157.3 mmol) of methyl 3-methyl-5-hydroxybenzoate and 16.2 ml of triethylamine dissolved in 500 ml of THF. The reaction medium is stirred for 16 hours at room temperature and worked-up as indicated in Example 1c, to give 55.12 g (86%) of the expected derivative in the form of a solid white product melting at 177-178°C.
^{1}H NMR ($CDCl_3$) d 1.31 (s, 6H), 1.34 (s, 6H); 1.72 (s, 4H), 2.38 (s, 3H), 3.90 (s, 3H), 7.42 (d, J = 8, 1H); 7.53 (dd, J = 8/2 Hz, 1H), 7.81 (br, NH), 7.89-7.96 (m, 3H); 8.32 (d, J = 8 Hz, 1H).

13b) Methyl 3-methyl-4-[N-tert-butoxycarbonyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthamido)]benzoate

The amide obtained in Example 13a (48 g, 126.5 mmol) is dissolved in 200 ml of DMF and is then treated with 7.6 g of sodium hydride (at 80%) introduced in small amounts. After the evolution of hydrogen has ceased, 55.2 g (2eq) of di-tert-butyl dicarbonate dissolved in 50 ml of DMF are added dropwise. The reaction medium is left stirring at room temperature for 16h. The reaction is poured into water, extracted with ether, washed and rinsed to give 59 g

(97%) of the expected derivative in the form of a pink oil. ^1H NMR ($CDCl_3$) d: 1.22 (s, 9H), 1.28 (s, 12H), 1.70 (s, 4H); 2.35 (s, 3H); 3.91 (s, 3H), 7.25 (d, 2Hz, 1H), 7.36 (d, 8Hz, 1H); 7.47 (dd, 8/2 Hz, 1H); 7.65 (d, 2Hz, 1H), 7.92 (dd, 8/2 Hz, 1H), 7.98 (s, 1H).

13c) Methyl 3-bromomethyl-4-[N-tert-butoxycarbonyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthamido)]benzoate

The derivative obtained in Example 13b (24.5 g, 51 mmol) is dissolved in carbon tetrachloride and treated with 9 g (50.6 mmol) of N-bromosuccinimide, 54 g (51 mmol) of sodium carbonate and 0.37 g (1.5 mmol) of benzoyl peroxide. The reaction is irradiated with a 1000 W lamp for 30 min. After evaporation, the residue is chromatographed on silica and eluted with a CH_2Cl_2/heptane mixture (20:80) to give 10.5 g (36%) of an amorphous product. ^1H NMR ($CDCl_3$) δ: 1.24 (s, 9H); 1.30 (s, 6H); 1.32 (s, 6H); 1.71 (s, 4H); 3.94 (s, 3H), 4.49 (s, 2H); 7.33 (d, J = 8Hz, 1H); 7.40 (d, J = 8Hz), 1H); 7.53 (dd, J = 8/2 Hz, 1H); 7.78 (s, 1H); 8.09 (dd, J = 2/8, 1H); 8.20 (s, 1H).

13d) Methyl 1-tert-butyloxycarbonyl-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthamido)-5-indolecarboxylate

The bromomethyl derivative obtained in Example 13c (9 g, 16.1 mmol) is dissolved in anhydrous THF (100 ml). 5 g (19.3 mmol) of triphenylphosphine are added to this solution. The reaction is refluxed for

4h. 2.94 g (19.3 mmol) of diazabicycloundecene are then added at room temperature and the mixture is left stirring at this temperature for one hour.

The reaction medium is poured into water, extracted with dichloromethane, washed, dried and evaporated. This residue is chromatographed on silica with 60:40 CH_2Cl_2/heptane as eluent, to give 4.8 g (65%) of the expected residue in the form of a white solid melting at 125-130°C. ^1H NMR ($CDCl_3$) δ: 1.26 (s, 9H), 1.31 (s, 12H); 1.72 (s, 4H); 3.95 (s, 3H); 6.59 (s, 1H); 7.13 (dd, J = 1.5/8 Hz, 1H); 7.3 (m, 2H), 8.01 (dd, J = 1.7/9 Hz, 1H), 8.23 (d, J = 11 Hz, 1H); 8.28 (d, 1.7 Hz, 1H).

13e) 2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-5-indolecarboxylic acid

A solution of 1.85 g (4 mmol) of the methyl ester are treated with 1.6 g (40 mmol) of sodium hydroxide in 25 ml of methanol. The reaction medium is refluxed for 13h and then left at room temperature for 15h. After evaporating off the methanol, the residue is taken up in water and is then acidified. This mixture is extracted with ethyl ether and the extracts are washed with water, dried and evaporated to give, after trituration from heptane, 1.34 g (96%) of a white powder melting at 265°C. ^1H NMR ($CDCl_3$) δ: 1.27 (s, 6H); 1.34 (s, 6H); 1.67 (s, 4H); 7.0 (s, 1H); 7.4 (d, J = 8 Hz, 1H); 7.45 (d, J = 8Hz, 1H); 7.62 (dd, J = 1.5/8.2 Hz, 1H); 7.73 (dd, J = 1.5/8.5 Hz, 1H); 7.82

(s, 1H); 8.2 (s, 1H); 11.82 (s, 1H).

B. FORMULATION EXAMPLES

1) ORAL ROUTE

(a) The following composition is prepared in the form of a 0.8 g tablet

Compound of Example 1	0.005 g
Pregelatinized starch	0.265 g
Microcrystalline cellulose	0.300 g
Lactose	0.200 g
Magnesium stearate	0.030 g

For the treatment of acne, 1 to 3 tablets are administered to an adult individual per day for 3 to 6 months depending on the severity of the case treated.

(b) A drinkable suspension intended for packaging in 5 ml ampules is prepared

Compound of Example 2	0.050 g
Glycerol	0.500 g
70% Sorbitol	0.500 g
Sodium saccharinate	0.010 g
Methyl para-hydroxybenzoate	0.040 g
Flavouring, q.s.	
Purified water q.s	5 ml

For the treatment of acne, 1 ampule is administered to an adult individual per day for 3 months depending on the severity of the case treated.

(c) The following formulation intended for packaging in gelatin capsules is prepared:

Compound of Example 3	0.025 g

Corn starch..... 0.060 g

Lactose q.s..... 0.300 g

The capsules used consist of gelatin, titanium oxide and a preserving agent.

In the treatment of psoriasis, 1 capsule is administered to an adult individual per day for 30 days.

2) TOPICAL ROUTE

(a) The following nonionic water-in-oil cream is prepared:

Compound of Example 4..... 0.100 g

Mixture of emulsifying lanolin alcohols, waxes and refined oils, sold by the company BDF under the name "anhydrous eucerin"..... 39.900 g

Methyl para-hydroxybenzoate..... 0.075 g

Propyl para-hydroxybenzoate..... 0.075 g

Sterile demineralized water q.s.....100.000 g

This cream is applied to psoriatic skin 1 to 2 times a day for 30 days.

(b) A gel is prepared by making the following formulation:

Compound of Example 5..... 0.050 g

Erythromycin base..... 4.000 g

Butylhydroxytoluene..... 0.050 g

Hydroxypropylcellulose sold by the company Hercules under the name "Klucel HF"..... 2.000 g

Ethanol (95° strength) q.s.....100,000 g

This gel is applied to a skin affected with

dermatosis or an acneic skin 1 to 3 times per day for 6 to 12 weeks depending on the severity of the case treated.

(c) An antiseborrhoea lotion is prepared by mixing together the following ingredients:

Compound of Example 6	0.030 g
Propylene glycol	5.000 g
Butylhydroxytoluene	0.100 g
Ethanol (95° strength) q.s	100.000 g

This lotion is applied twice a day to a seborrhoeic scalp and a significant improvement is observed within a period of 2 to 6 weeks.

(d) A cosmetic composition to counter the harmful effects of the sun is prepared by mixing together the following ingredients:

Compound of Example 7	1.000 g
Benzylidenecamphor	4.000 g
Fatty acid triglycerides	31.000 g
Glyceryl monostearate	6.000 g
Stearic acid	2.000 g
Cetyl alcohol	1.200 g
Lanolin	4.000 g
Preserving agents	0.300 g
Propylene glycol	2.000 g
Triethanolamine	0.500 g
Fragrance	0.400 g
Demineralized water q.s	100.000 g

This composition is applied daily and makes

it possible to combat photo-induced ageing.

(e) The following nonionic oil-in-water cream is prepared:

Compound of Example 8	0.500 g
Vitamin D3	0.020 g
Cetyl alcohol	4.000 g
Glyceryl monostearate	2.500 g
PEG 50 stearate	2.500 g
Karite butter	9.200 g
Propylene glycol	2.000 g
Methyl para-hydroxybenzoate	0.075 g
Propyl para-hydroxybenzoate	0.075 g
Sterile demineralized water q.s	100.000 g

This cream is applied to a psoriatic skin 1 to 2 times a day for 30 days.

(f) A topical gel is prepared by mixing together the following ingredients:

Compound of Example 9	0.050 g
Ethanol	43.000 g
α-Tocopherol	0.050 g
Carboxyvinyl polymer sold under the name "Carbopol 941" by the company "Goodrich"	0.500 g
Triethanolamine as a 20% aqueous solution by weight	3.800 g
Water	9.300 g
Propylene glycol q.s	100.000 g

This gel is applied in the treatment of acne

1 to 3 times a day for 6 to 12 weeks depending on the severity of the case treated.

(g) A lotion for combating hair loss and for the regrowth of the hair is prepared by mixing together the following ingredients:

Compound of Example 10	0.05 g
Compound sold under the name "Minoxidil"	1.00 g
Propylene glycol	20.00 g
Ethanol	34.92 g
Polyethylene glycol (molecular mass = 400)	40.00 g
Butylhydroxyanisole	0.01 g
Butylhydroxytoluene	0.02 g
Water q.s	100.00 g

This lotion is applied twice a day for 3 months to a scalp which has suffered considerable hair loss.

(h) An antiacne cream is prepared by mixing together the following ingredients:

Compound of Example 12	0.050 g
Retinoic acid	0.010 g
Mixture of glyceryl stearate and of polyethylene glycol stearate (75 mol) sold under the name "Gelot 64" by the company "Gattefosse"	15.000 g

Palm kernel oil polyoxyethylenated with 6 mol of ethylene oxide, sold under the name "Labrafil

M2130 CS" by the company "Gattefosse".... 8.000 g
Perhydrosqualene..... 10.000 g
Preserving agents ..... qs
Polyethylene glycol (molecular mass = 400)..... 8.000 g
Disodium salt of ethylenediaminetetraacetic acid..... 0.050 g
Purified water q.s.....100.000 g

This cream is applied to a skin affected with dermatosis or an acneic skin 1 to 3 times a day for 6 to 12 weeks.

(i) An oil-in-water cream is prepared by making the following formulation:

Compound of Example 13..... 0.020 g
Betamethasone 17-valerate..... 0.050 g
S-Carboxymethylcysteine..... 3.000 g
Polyoxyethylene stearate (40 mol of ethylene oxide) sold under the name "Myrj 52" by the company "Atlas"..... 4.000 g
Sorbitan monolaurate polyoxyethylenated with 20 mol of ethylene oxide, sold under the name "Tween 20" by the company "Atlas"..... 1.800 g
Mixture of glyceryl mono- and distearate sold under the name "Géléol" by the company "Gattefosse"..... 4.200 g
Propylene glycol..... 10.000 g

Butylhydroxyanisole..... 0.010 g
Butylhydroxytoluene..... 0.020 g
Cetostearyl alcohol..... 6.200 g
Preserving agents ..... q.s.
Perhydrosqualene..... 18.000 g
Mixture of caprylic/capric triglycerides sold under the name "Miglyol 812" by the company "Dynamit Nobel"..... 4.000 g
Triethanolamine (99% by weight)..... 2.500 g
Water q.s.....100.000 g

This cream is applied twice a day to a skin affected by dermatosis, for 30 days.

(j) The following oil-in-water type cream is prepared:

Lactic acid..... 5.000 g
Compound of Example 11..... 0.020 g
Polyoxyethylene stearate (40 mol of ethylene oxide) sold under the name "Myrj 52" by the company "Atlas"..... 4.000 g
Sorbitan monolaurate polyoxyethylenated with 20 mol of ethylene oxide, sold under the name "Tween 20" by the company "Atlas"... 1.800 g
Mixture of glyceryl mono- and distearate sold under the name "Geleol" by the company "Gattefosse"..... 4.200 g
Propylene glycol..... 10.000 g
Butylhydroxyanisole..... 0.010 g
Butylhydroxytoluene..... 0.020 g

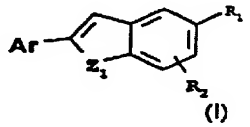
Cetostearyl alcohol..... 6.200 g
Preserving agents ..... q.s.
Perhydrosqualene..... 18.000 g
Mixture of caprylic/capric triglycerides
sold under the name "Miglyol 812" by the
company "Dynamit Nobel"..... 4.000 g
Water q.s.....100.000 g

This cream is applied once a day and helps to counter ageing, whether this is photo-induced or chronological ageing.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprising" is used in the sense of "including", i.e. the features specified may be associated with further features in various embodiments of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

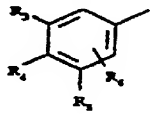
1. Compounds, characterized in that they correspond to the general formula (I) below:



(I)

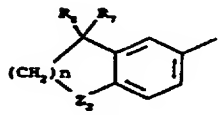
in which:

Ar represents a radical chosen from the radicals of formulae (II)-(IV) below:



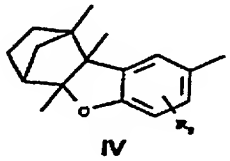
II

R_3, R_4, R_5 and R_6 having the meanings given below,



III

n, Z_2, R_7 and R_8 having the meanings given below,



IV

R_9 having the meaning given below,

Z_1 represents an oxygen or sulphur atom or a radical NR',

R' having the meaning given below,

Z_2 represents $C(R_7R_8)$, O, NR', S, SO or SO_2,

R_7, R_8 and R' having the meanings given below,

R_1 represents

(i) a $-CH_3$ radical,

(ii) a radical $-(CH_2)_m-O-R_{10}$,

(iii) a radical $-CH_2-O-CO-R_{11}$

(iv) a radical $-(CH_2)_x-CO-R_{12}$

(v) a radical $-(CH_2)_x-CO-OR_{13}$

R_{10}, R_{11}, R_{12} and R_{13}, m, x and t having the meanings given below,

R_2 represents a hydrogen atom, a halogen atom, a linear or branched alkoxy radical of 1 to 20 carbon atoms or an $-O-CH_2-O-CH_2-CH_2-O-CH_3$ radical,

R_3 and R_5, which may be identical or different, represent a hydrogen atom, an alkyl radical or a cycloalkyl radical,

with the following conditions:

- R_3 and R_5 do not simultaneously represent a hydrogen atom,
- when R_3 or R_5 represents an adamantyl radical, then Z_1 is other than an oxygen atom,

R_4 represents an $-O-CH_2-O-CH_2-CH_2-O-CH_3$ radical, a radical $-(Y)_q-(CH_2)_s-R_{14}$, a radical $-(CH_2)_z-Y-(CH_2)_s-R_{14}$ or a radical $-CH=CH-(CH_2)_w-R_{14}$,

Y and R_{14} having the meanings given below,

q, z, s, w, which may be identical or different, having the meanings given below,

R_6 represents a hydrogen atom, a halogen atom, a linear or branched alkoxy radical of 1 to 20 carbon atoms or a radical $-O-CH_2-O-CH_2-CH_2-O-CH_3$,

R_7 and R_8, which may be identical or different, represent a lower alkyl radical,

R_9 represents a hydrogen atom, a halogen atom, a linear or branched alkoxy radical of 1 to 20 carbon atoms or an $-O-CH_2-O-CH_2-CH_2-O-CH_3$ radical,

R_{10} represents a hydrogen or a lower alkyl radical,

R_{11} represents a lower alkyl radical,

R_{12} represents a hydrogen atom, a lower alkyl radical or a radical $-N(R",R"')$,

R" and R"' having the meanings given below,

R_{13} represents a hydrogen atom, a linear or branched alkyl radical of 1 to 20 carbon atoms, an alkenyl radical or a mono- or polyhydroxyalkyl radical,

R_{14} represents a radical chosen from:

(i) a hydrogen atom,

(ii) a lower alkyl radical,

(iii) an alkenyl radical,

(iv) an alkynyl radical,

(v) a cycloaliphatic radical containing from 3 to 6 carbon atoms,

(vi) a mono- or polyhydroxyalkyl radical, it being possible for the hydroxyl groups to be optionally protected in the form of methoxy,

acetoxy or acetonide,

(vii) a radical CO-R_{12},

(viii) a radical COO-R_{13},

(ix) a hydroxyl radical, a radical O-R_{15} or O-CO-R_{15}, on the condition that R_4 represents a radical -$(Y)_q$-$(CH_2)_s$-R_{14} where q is equal to 0,

Y and R_{15} having the meanings given below,

q and s having the meanings given below,

R_{15} represents a lower alkyl radical,

R' represents a hydrogen atom, a lower alkyl radical or a protecting group for the amine function,

R" and R"', which may be identical or different, represent a hydrogen atom, a lower alkyl radical or a mono- or polyhydroxyalkyl radical, or alternatively R" and R"', taken together, form a heterocycle,

Y represents S, O or S(O)t,

t having the meaning given below,

m represents an integer which can take a value ranging from 0 to 2,

n represents an integer which can take the value 1 or 2,

q represents an integer which can take the value 0 or 1,

s represents an integer which can take a value ranging from 0 to 12,

t represents an integer which can take a value

ranging from 0 to 3,

w represents an integer which can take a value ranging from 0 to 10,

x represents an integer which can take a value ranging from 0 to 2,

z represents an integer which can take the value 1, 2 or 3,

and the optical and geometrical isomers of the said compounds of formula (I), as well as the salts thereof.

2. Compounds according to Claim 1, characterized in that they are in the form of salts of an alkali metal or alkaline-earth metal, of zinc, of an organic amine or of an inorganic or organic acid.

3. Compounds according to either of Claims 1 and 2, characterized in that the lower alkyl radicals are chosen from the methyl, ethyl, isopropyl, n-butyl and tert-butyl radicals.

4. Compounds according to one of the preceding claims, characterized in that the cycloalkyl radical optionally substituted with one or more halogen atoms or one or more hydroxyl radicals corresponds to an adamantyl radical or a 1-methylcyclohexyl radical.

5. Compounds according to one of the preceding claims, characterized in that the mono-hydroxyalkyl radicals are chosen from the 2-hydroxy-ethyl, 2-hydroxypropyl and 3-hydroxypropyl radicals.

6. Compounds according to one of the preceding claims, characterized in that the poly-

hydroxyalkyl radicals are chosen from the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl and 2,3,4,5-tetrahydroxypentyl radicals or the pentaerythritol residue.

7. Compounds according to any one of the preceding claims, characterized in that the heterocyclic radicals are chosen from the group consisting of piperidino, morpholino, pyrrolidino and piperazino radicals, optionally substituted in position 4 with a C_1-C_6 alkyl radical or with a mono- or polyhydroxyalkyl radical.

8. Compounds according to Claim 1, characterized in that they are taken, alone or as mixtures, from the group consisting of:

- methyl 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)furancarboxylate,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)furancarboxylic acid,
- methyl 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)thiophenecarboxylate,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-benzo(b)thiophenecarboxylic acid,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-indolecarboxylic acid,
- methyl 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-2-naphthyl)-5-indolecarboxylate,
- 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)benzo(b)thiophene-5-carboxylic

acid,

- methyl 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)benzo(b)thiophene-5-carboxylate,
- 2-(1,2,3,4,4a,9b-hexahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)benzo(b)furan-5-carboxylic acid,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-methoxy-2-naphthyl)-5-benzo(b)furancarboxylic acid,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-methoxy-2-naphthyl)-5-benzo(b)thiophenecarboxylic acid,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-n-propyloxy-2-naphthyl)-5-benzo(b)thiophenecarboxylic acid,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-n-propyloxy-2-naphthyl)-5-benzo(b)furancarboxylic acid,
- 2-(5,6,7,8-tetrahydro-5,5,8,8,-tetramethyl-3-n-heptyloxy-2-naphthyl)-5-benzo(b)furancarboxylic acid.

9. Compounds according to Claim 1, characterized in that they have at least one, and preferably all, of the following characteristics:

- R_1 is a radical $-(CH_2)_x-CO-R_{12}$ or $-(CH_2)x-CO-O-R_{13}$
- R_2 is a hydrogen,
- Z_1 is an oxygen or sulphur atom
- Ar is chosen from

the radical IV in which:

- R_9 is a hydrogen atom,

or the radical III in which:

- Z_2 is a radical $C(R_7, R_8)$
- n=2

10. Compounds according to any one of the preceding claims, for use as medicinal products.

11. Compounds according to Claim 10, for use as medicinal products intended for treating dermatological complaints linked to a keratinization disorder which has a bearing on differentiation and on proliferation, in particular for treating common acne, comedones, polymorphonuclear leukocytes, acne rosacea, nodulocystic acne, acne conglobata, senile acne and secondary acnes such as solar, medicational or occupational acne; for treating other types of keratinization disorder, in particular ichthyoses, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leukoplasias and leukoplasiform states, and cutaneous or mucous (buccal) lichen; for treating other dermatological complaints associated with a keratinization disorder with an inflammatory and/or immunoallergic component and, in particular, all forms of psoriasis, whether this is cutaneous, mucous or ungual psoriasis, and even psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema or respiratory atopy or even gingival hypertrophy; the compounds may also be used in certain inflammatory complaints which do not exhibit any keratinization disorder; for treating all dermal or epidermal

proliferations, whether these are benign or malignant and whether or not they are of viral origin, such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatoses and proliferations which may be induced by ultraviolet radiation, in particular in the case of basocellular and spinocellular epithelioma; for treating other dermatological disorders such as bullosis and collagen diseases; for treating certain ophthalmological disorders, in particular corneopathies; for repairing or combating ageing of the skin, whether this is photo-induced or chronological ageing, or for reducing actinic keratoses and pigmentations, or all pathologies associated with chronological or actinic ageing; for preventing or curing the stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy; for preventing or treating cicatrization disorders or for preventing or repairing stretchmarks; for promoting cicatrization; for combating disorders of sebaceous function such as acneic hyperseborrhoea or simple seborrhoea; for the treatment or prevention of cancerous or precancerous states, more particularly promyelocytic leukaemias; for the treatment of inflammatory complaints such as arthritis; for the treatment of any skin complaint or general complaint of viral origin; for the prevention or treatment of alopecia; for the treatment of dermatological

complaints having an immunological component; for the treatment of complaints of the cardiovascular system such as arteriosclerosis; for the treatment of skin disorders due to exposure to UV radiation.

12. Pharmaceutical composition, characterized in that it comprises, in a pharmaceutically acceptable support, at least one of the compounds as defined in any one of Claims 1 to 9.

13. Composition according to Claim 12, characterized in that the concentration of compound(s) according to one of Claims 1 to 9 is between 0.001% and 5% by weight relative to the whole composition.

14. Cosmetic composition, characterized in that it comprises, in a cosmetically acceptable support, at least one of the compounds as defined in any one of Claims 1 to 9.

15. Composition according to Claim 14, characterized in that the concentration of compound(s) according to one of Claims 1 to 9 is between 0.001% and 3% by weight relative to the whole composition.

16. Use of a cosmetic composition as defined in either of Claims 14 and 15, for body or hair hygiene.

Dated this 31st day of May 1999
GALDERMA RESEARCH & DEVELOPMENT, S.N.C.
By their Patent Attorneys
GRIFFITH HACK
Fellows Institute of Patent and
Trade Mark Attorneys of Australia

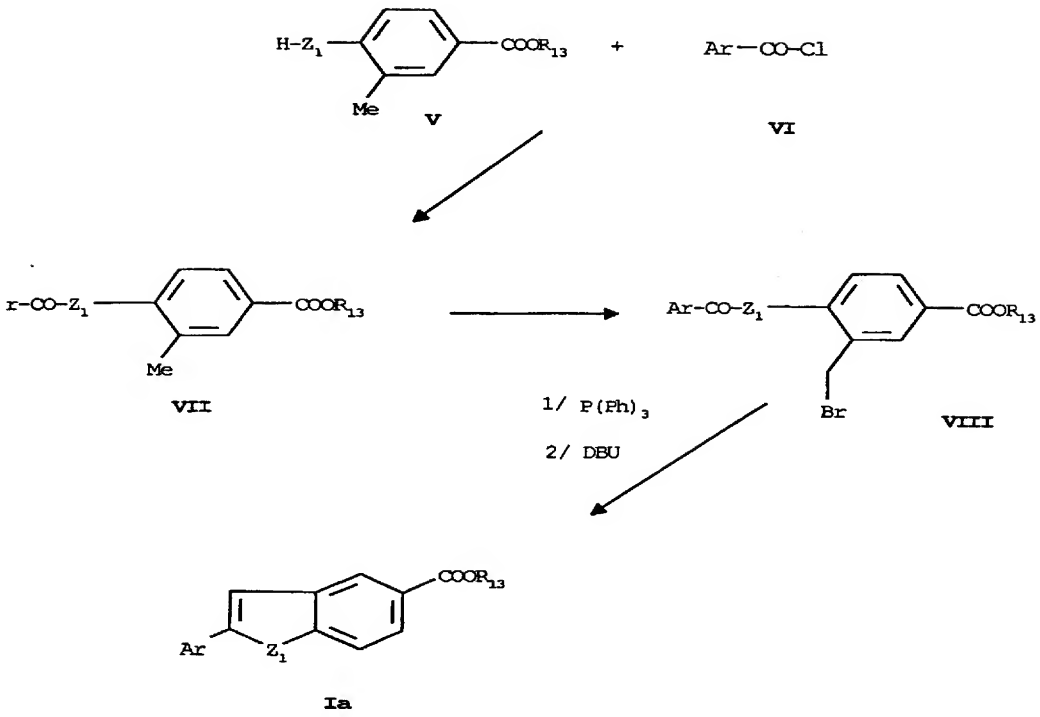

H-Z1
COOR13
Me
V
+
Ar—CO—Cl
VI
r-CO-Z1
COOR13
Me
VII
Ar-CO-Z1
COOR13
Br
VIII
1/ P(Ph)3
2/ DBU
COOR13
Ar
Z1
Ia

Figure 1

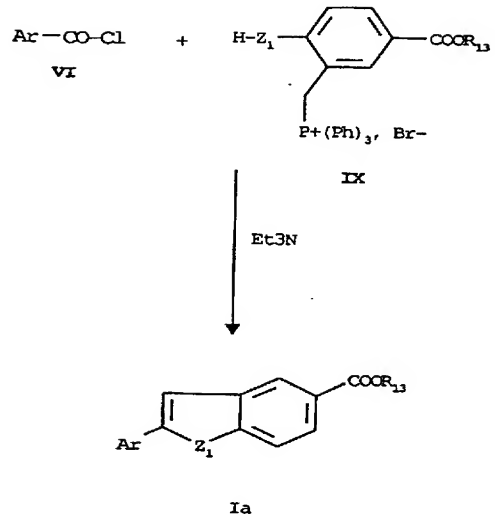


Figure 2